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(21) International Application Number: PCT/US99/30405 (22) International Filing Date: 20 December 1999 (20.12.99) (30) Priority Data: 60/113,303 22 December 1998 (22.12.98) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BACH, Nicholas, James [US/US]; 7215 South Meridian Street, Indianapolis, IN 46217 (US). HARPER, Richard, Waltz [US/US]; 7310 Sylvan Ridge Road, Indianapolis, IN 46240 (US). KINNICK, Michael, Dean [US/US]; 343 Southcreek Drive South, Indianapolis, IN 46217 (US). LIN, Ho-Shen [US/US]; 8128 Trevellian Way, Indianapolis, IN 46217 (US). MORIN, John, Michael, Junior [US/US]; 9 Roselawn Avenue, Brownsburg, IN 46112 (US). RICHETT, Michael, Enrico [US/US]; 5832 Baron Court, Indianapolis, IN 46250 (US). (74) Agents: BENJAMIN, Roger, S. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NOVEL sPLA ₂ INHIBITORS (57) Abstract A class of novel indole is disclosed together with the use of such compounds for inhibiting sPLA ₂ mediated release of fatty acids for treatment of inflammatory diseases such as septic shock.		

Novel sPLA₂ Inhibitors

Field of the Invention

This invention relates to novel indole compounds
5 useful for inflammatory diseases.

Background of the Invention

The structure and physical properties of human non-pancreatic secretory phospholipase A₂ (hereinafter
10 called, "sPLA₂") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A₂ Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A₂" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April
20 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

25 It is believed that sPLA₂ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA₂ mediated release of fatty acids (e.g., arachidonic acid). Such
30 compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA₂; such as sepsis or rheumatoid arthritis.

It is desirable to develop new compounds and
35 treatments for sPLA₂ induced diseases.

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Summary of the Invention

This invention is a novel class of indole oxime
amide compounds having potent and selective
5 effectiveness as inhibitors of mammalian sPLA₂.

This invention is also the use of indole oxime
amide compounds in the treatment and prevention of
Inflammatory Diseases.

This invention is also the use of novel of indole
10 oxime amide compounds to inhibit mammalian sPLA₂
mediated release of fatty acids.

This invention is also a pharmaceutical
compositions containing indole oxime amide compounds of
the invention.

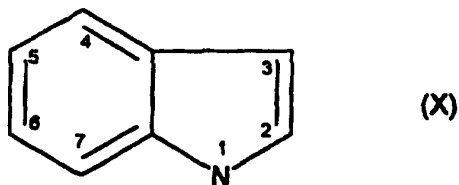
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Definitions:

The term, "Inflammatory Diseases" refers to
diseases such as inflammatory bowel disease, sepsis,
20 septic shock, adult respiratory distress syndrome,
pancreatitis, trauma-induced shock, bronchial asthma,
allergic rhinitis, rheumatoid arthritis, cystic
fibrosis, stroke, acute bronchitis, chronic bronchitis,
acute bronchiolitis, chronic bronchiolitis,
25 osteoarthritis, gout, spondylarthropathris, ankylosing
spondylitis, Reiter's syndrome, psoriatic arthropathy,
enteropathric spondylitis, Juvenile arthropathy or
juvenile ankylosing spondylitis, Reactive arthropathy,
infectious or post-infectious arthritis, gonococcal
30 arthritis, tuberculous arthritis, viral arthritis,
fungal arthritis, syphilitic arthritis, Lyme disease,
arthritis associated with "vasculitic syndromes",
polyarteritis nodosa, hypersensitivity vasculitis,
Luegenec's granulomatosis, polymyalgin rheumatica,
35 joint cell arteritis, calcium crystal deposition

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- arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint
- 5 disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and
- 10 other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis and related diseases which comprises administering to a
- 15 mammal in need of such treatment a therapeutically effective amount of the compound of formula I in an amount sufficient to inhibit sPLA₂ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.
- 20 The term, "indole nucleus" refers to a nucleus (having numbered positions) with the structural formula (X):



- 25 The indole compounds of the invention employ certain defining terms as follows:
- The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such

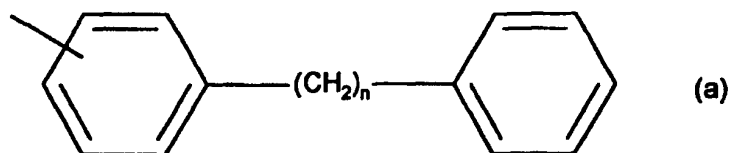
-4-

as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, sec-butyl, n-pentyl, and n-hexyl. The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group containing only carbon and hydrogen. The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, triazolyl, isoxazolyl, oxazolyl, phenylimidazolyl, indolyl, carbazolyl, thiazolyl, thiadiazolyl, imidazo(1,2-a)pyridinyl, norharmanyl, azaindolyl, benzofuranyl, dibenzothienyl, indazolyl, imidazolyl, oxazolyl, benzoxazolyl, anthranilyl, purinyl, pyridinyl, dipyridinyl, phenylpyrimidinyl, benzylpyridinyl, pyrimidinyl, quinolinyl, phthalazinyl, triazinyl, morpholino, thiomorpholino, homopiperazinyl, quinazolinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, oxacanyl, 1,3-tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny, hexamethyleneiminium, heptamethyleneiminium, piperazinyl and quinoxaliny.

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The term, "carbocyclic radical" refers to radicals derived from a saturated or unsaturated, substituted or unsubstituted 5 to 14 membered organic nucleus whose ring forming atoms (other than hydrogen) are solely carbon atoms. Typical carbocyclic radicals are cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by the formula (a):



where n is a number from 1 to 8.

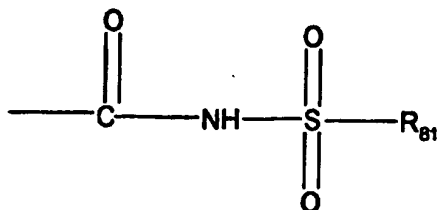
The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈

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alkyl), benzyloxy, phenoxy, phenylthio, $-(\text{CONHSO}_2\text{R})$, $-\text{CHO}$, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(\text{CH}_2)_n\text{-CO}_2\text{H}$, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-\text{SO}_3\text{H}$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

The term, "organic substituent" refers to a monovalent radical consisting of carbon and hydrogen with or without oxygen, nitrogen, sulfur, halogen, or other elements. Illustrative organic substituents are $\text{C}_1\text{-C}_8$ alkyl, aryl, $\text{C}_7\text{-C}_{14}$ aralkyl, $\text{C}_7\text{-C}_{14}$ alkaryl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_8$ alkoxyalkyl and these groups substituted with halogen, $-\text{CF}_3$, $-\text{OH}$, $\text{C}_1\text{-C}_8$ alkyl, amino, carbonyl, and $-\text{CN}$.

The term, "acylsulfonamide group" is an (acidic group) represented by the formula:



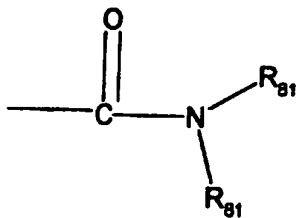
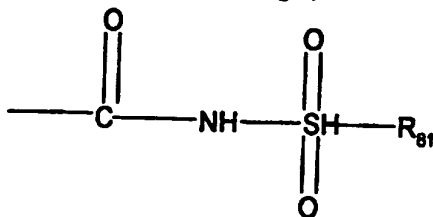
where R_{81} is an organic substituent or the radical $-\text{CF}_3$.

The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

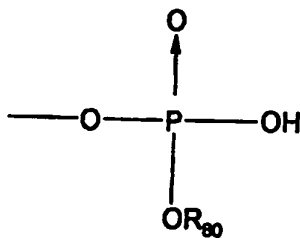
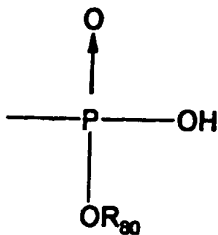
The term, "(acidic group)" means an organic group which when attached to an indole nucleus, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

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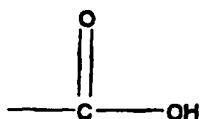
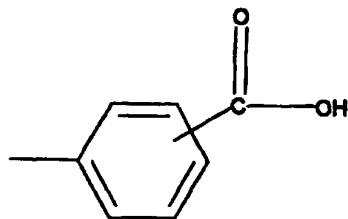
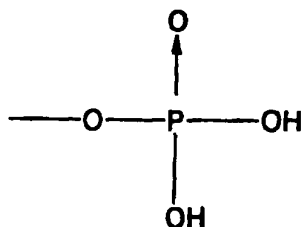
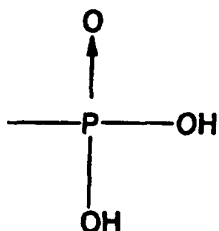
-5-tetrazolyl,

-SO₃H,

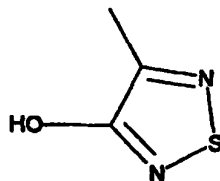
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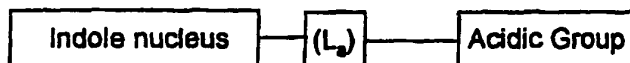
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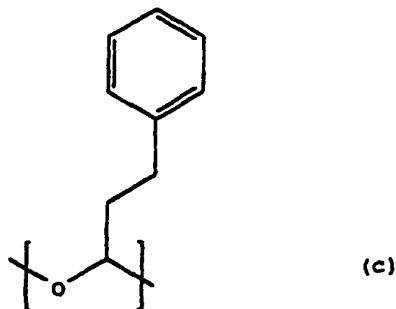
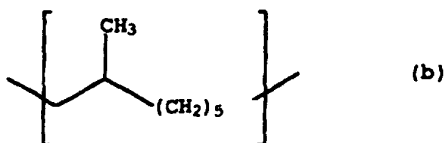
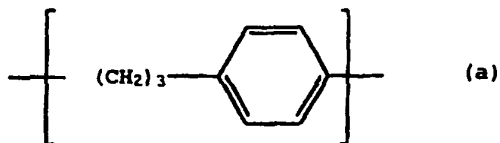
where n is 1 to 8, R₈₀ is a metal or C₁-C₈ and R₈₁ is
 5 an organic substituent or -CF₃.

The words, "acid linker" refer to a divalent
 linking group symbolized as, -(L_a)-, which has the
 function of joining the 4 or 5 position of the indole
 nucleus to an acidic group in the general relationship:

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The words, "acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_a)-$ that connects the 4 or 5 position of the indole nucleus with the acidic group. The presence of a carbocyclic ring in $-(L_a)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_a)-$. Illustrative acid linker groups are;



15

wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

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The terms, "mammal" and "mammalian" include human.

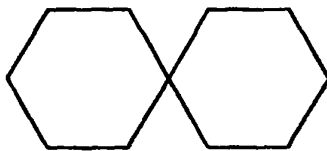
The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-$.

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, and $-\text{CH}=\text{CH}_2$.

The term "oxime amide" means the radical,
 $-\text{C}=\text{NOR}-\text{C}(\text{O})\text{NH}_2$

The term "thio-oxime amide" means the radical
 $-\text{C}=\text{NOR}-\text{C}(\text{S})-\text{NH}_2$.

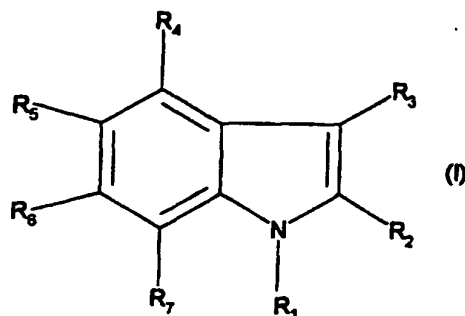
The term "spiro[5.5]undecanyl" refers to the group
represented by the formula;



The indole Compounds of the Invention:

The compounds of the invention have the general formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof;

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wherein ;

R_1 is selected from groups (a), (b) and (c)

5 wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

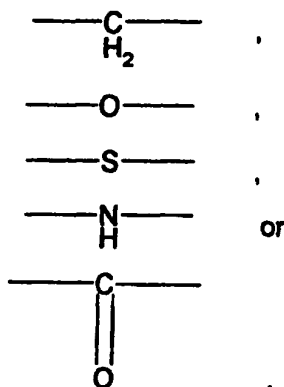
(b) is a member of (a) substituted with one
10 or more independently selected non-interfering substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a)
15 or (b);

R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

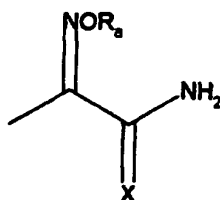
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected
20 from:

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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

5



wherein, X is oxygen or sulfur; and R₄ is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R₄ and R₅ are independently selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8, provided, that
15 at least one of R₄ and R₅ must be the group, -(L_a)-(acidic group);

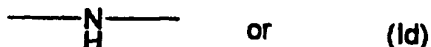
R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering
20 substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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Preferred Subgroups of Compounds of Formula (I):

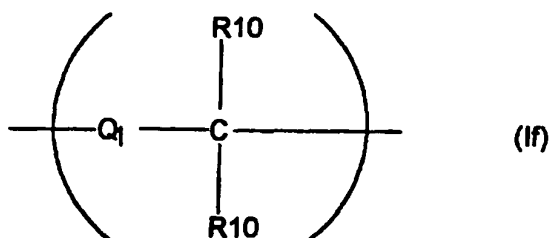
I. Preferred R_1 substituents:

- A preferred subclass of compounds of formula (I)
 5 are those where for R_1 the divalent linking group
 $-(L_1)-$ is a group represented by any one of the
 following formulae (Ia), (Ib), (Ic), (Id), (Ie), or
 (If):



10

or



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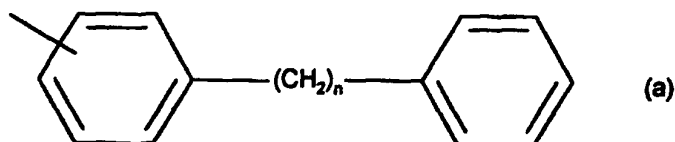
where Q_1 is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is
 independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or
 C_{1-8} alkoxy.

20

Particularly preferred as the linking group $-(L_1)-$
 of R_1 is an alkylene chain of 1 or 2 carbon atoms,
 namely, $-(CH_2)-$ or $-(CH_2-CH_2)-$.

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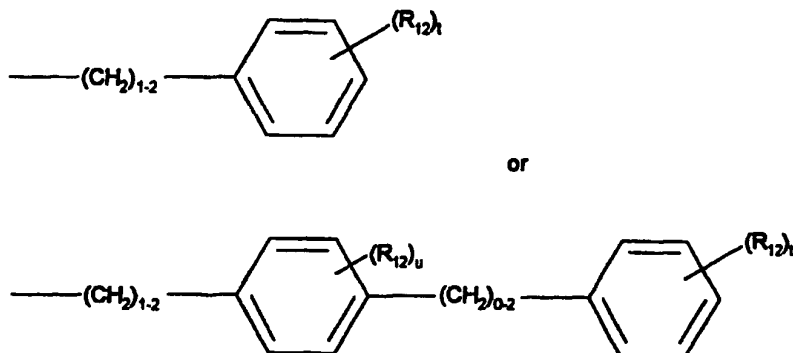
The preferred group for R_{11} is a substituted or unsubstituted group selected from the group consisting of C_5 - C_{14} cycloalkyl, C_5 - C_{14} cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xlylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by the formula (a);



10. where n is a number from 1 to 8.

Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of

15



where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8 \text{ alkyl})$ and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

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II. Preferred R₂ substituents:

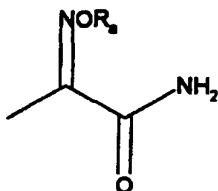
R₂ is preferably selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-
 5 (C₁-C₃ alkyl), -S-(C₁-C₃ alkyl), -C₃-C₄ cycloalkyl -CF₃, halo, -NO₂, -CN, -SO₃. Particularly preferred R₂ groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃.

10

III. Preferred R₃ substituents:

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

15 Another preferred subclass of compounds of formula (I) are those wherein Z is a oxime amide group.

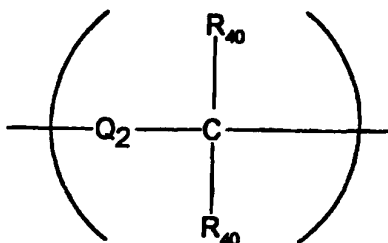


20 Most preferred are compounds of formula (I) wherein R₃ is an oxime amide group and R_a is hydrogen, methyl or ethyl. For the group R₃ it is preferred that the linking group -(L₃)- be a bond.

25 IV. Preferred R₄ substituents:

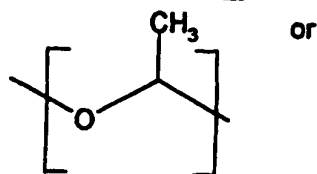
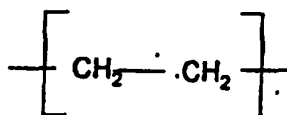
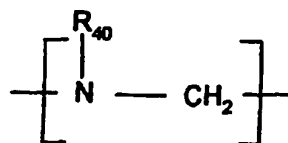
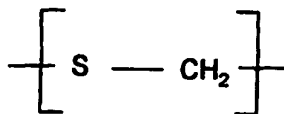
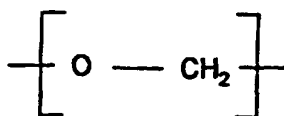
Another preferred subclass of compounds of formula (I) are those wherein R₄ is a substituent having an acid linker with an acid linker length of 2 or 3 and
 30 the acid link r group, -(L₄)-, for R₄ is selected from a group represented by the formula;

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where Q₂ is selected from the group -(CH₂)-, -O-, -NH-,
 5 -C(O)-, and -S-, and each R₄₀ is independently selected
 from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈
 alkoxy, aralkyl, and halo. Most preferred are
 compounds where the acid linker, -(L₄)-, for R₄ is
 selected from the specific groups;

10



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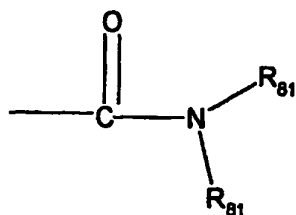
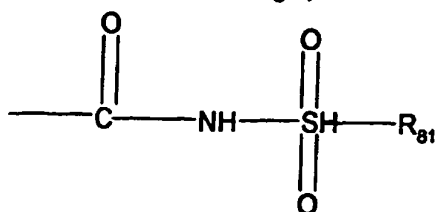
where R_{40} is hydrogen or C_1 - C_8 alkyl.

Preferred as the (acidic group) in the group R_4 are acidic groups selected from:

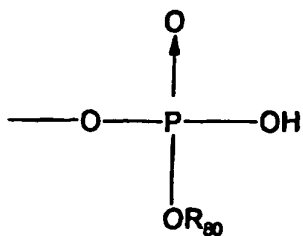
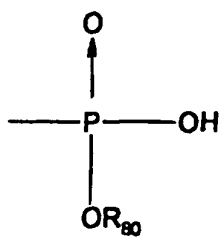
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-5-tetrazolyl,

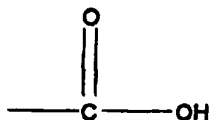
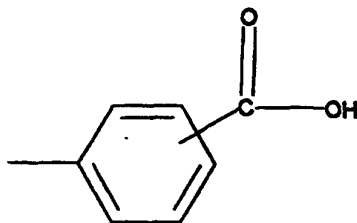
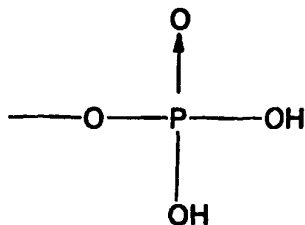
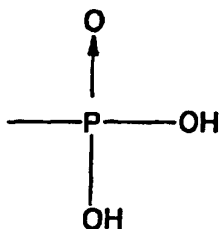
-SO₃H,



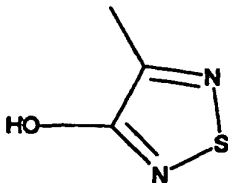
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-18-



or



where R₈₀ is a metal or C₁-C₈ and R₈₁ is an organic
 5 substituent or -CF₃. A salt or a prodrug derivative of
 the (acidic group) is also a suitable substituent.

Particularly preferred are acidic groups selected
 from:

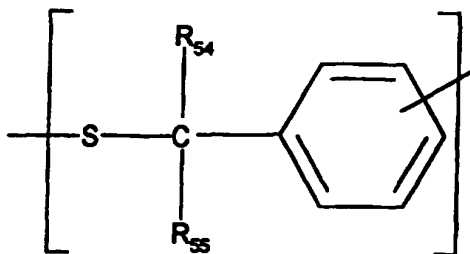
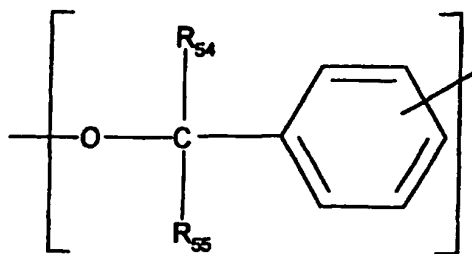
-19-

— CO₂H ,— SO₃H ,— P(O)(OH)₂ ,

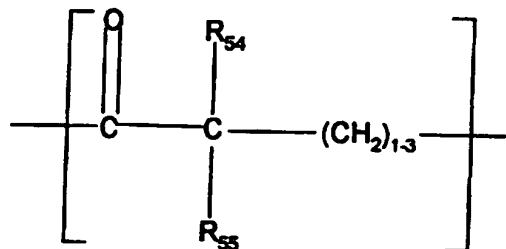
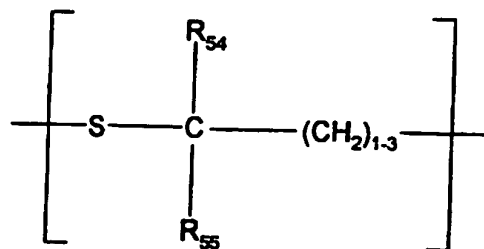
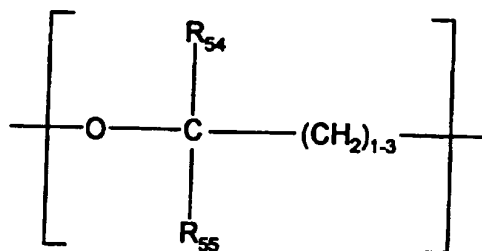
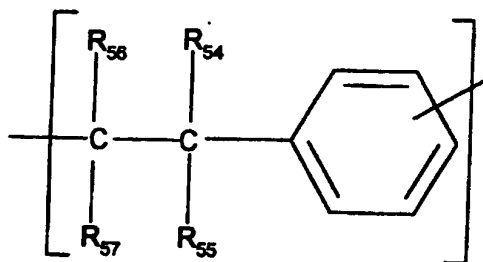
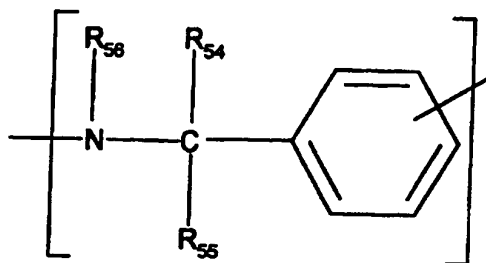
or salt, and prodrug (e.g., ester, amide) derivatives thereof. The most preferred acidic group
 5 in the compounds of the invention is a carboxylic acid group, -CO₂H.

V. Preferred R₅ Substituents:

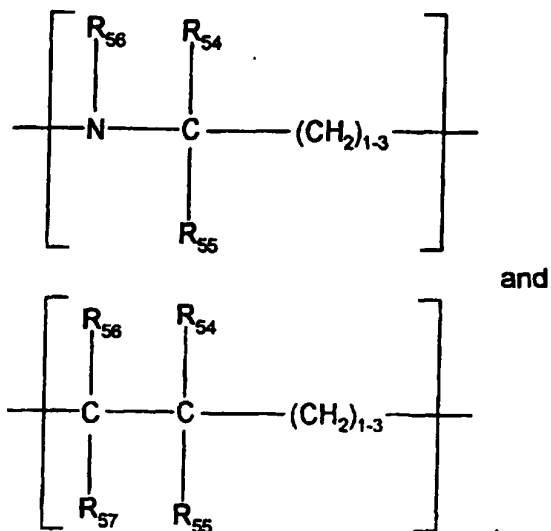
Preferred acid linker, -(L_a)-, for R₅ is selected from
 10 the group consisting of;



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wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

VI. Preferred (acidic group) for R₄ and/or R₅ substitutions:

At least one of R₄ and R₅ must be the group, -(L_a)-(acidic group). The preferred (acidic group) on the group -(L_a)-(acidic group) of R₄ or R₅ is selected from -CO₂H, -SO₃H, or -P(O)(OH)₂. In addition, it is preferred that only one R₄ or R₅ substituents be the group, -(L_a)-(acidic group).

The preferred (acidic group) is the same as those set out in the prior section describing R₄ substituents.

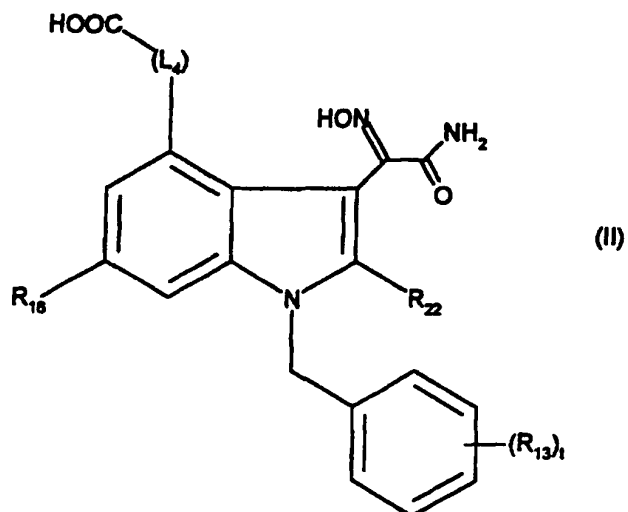
V. Preferred R₆ substituents:

Another preferred subclass of compounds of formula (I) are those wherein for R₆ the non-interfering substituent is methyl, ethyl, propyl,

-22-

- isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆ haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.
- Most preferred as non-interfering substituents are methyl, ethyl, propyl, and isopropyl.
- Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

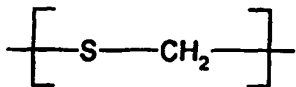
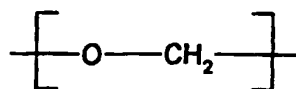
-23-



wherein ;

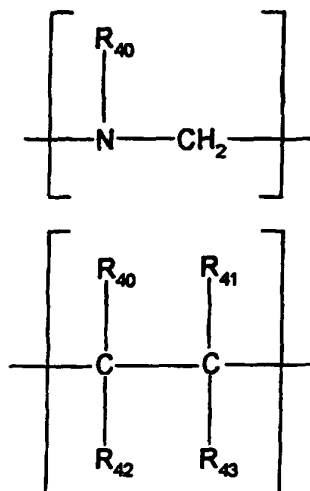
- 5 R₂₂ is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃;

- (L₄) - is a divalent group selected from;

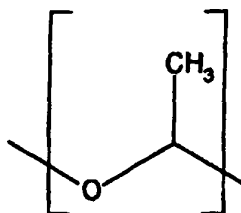


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or



where R_{40} , R_{41} , R_{42} , and R_{43} are each independently
 5 selected from hydrogen or C₁-C₈ alkyl.

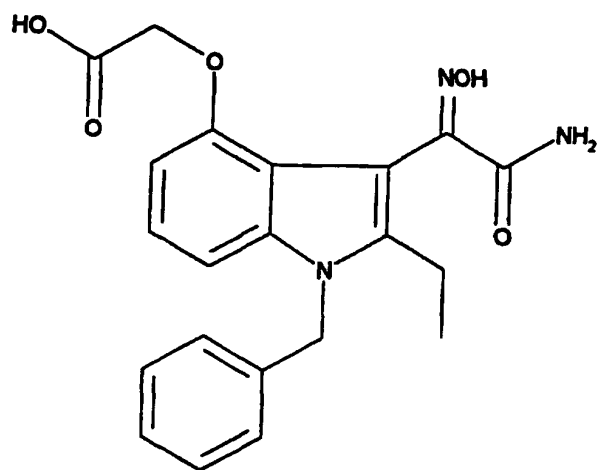
R_{16} is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈
 alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈
 hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈
 10 alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈, phenyl,
 halophenyl, hydroxyalkyl, and halo, and t is an integer
 from 0 to 5.

Preferred specific compounds (and all
 pharmaceutically acceptable salts, solvates and prodrug
 15 derivatives thereof) which are illustrative of the
 compounds of the invention are as follow:

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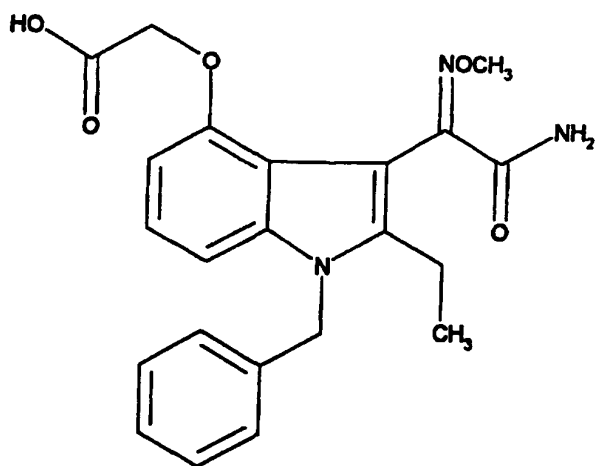
Compound C1



(C1)

5

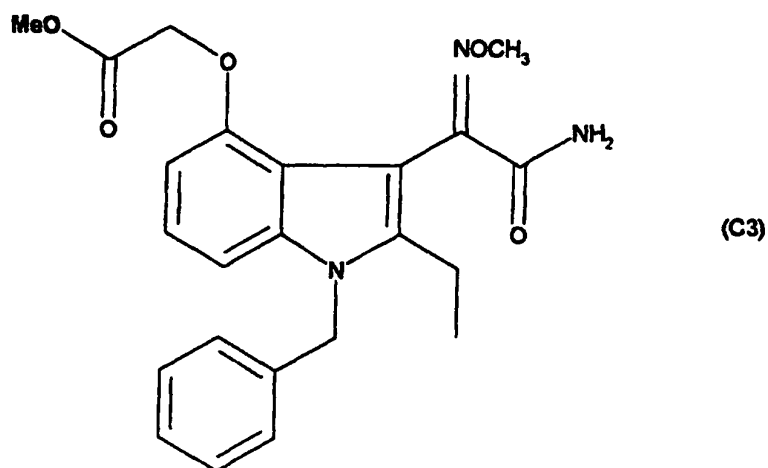
Compound C1



(C2)

10

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- The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin. For example, the (acidic group) of the substituent R_4 of Formula I may be selected as $-CO_2H$ and salts may be formed by reaction with appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium and potassium salt.
- Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the

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compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable
5 organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate,
10 gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinolate, bromide, chloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, malseate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate,
15 oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one
20 or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic
25 mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in
30 the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to
35 mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be

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reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and
5 different solubilities can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under
10 physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility,
15 tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the
20 parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it
25 is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.
30 N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich

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Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

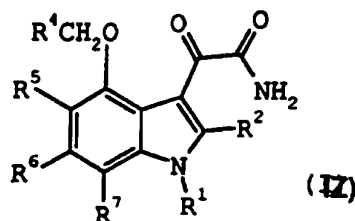
Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

10 Method of Making the Compounds of the Invention:

The synthesis of the indole compounds of the invention (viz., Compounds of Formulae I and II) can be accomplished by well known methods as recorded in the chemical literature. In particular, the indole starting materials may be prepared by the synthesis schemes taught in US Patent No. 5,654,326; the disclosure of which is incorporated herein by reference. Another method of making 1H-indole-3-glyoxylamide sPLA₂ inhibitors is described in United States Patent Application Serial No. 09/105381, filed June 26, 1998 and titled, "Process for Preparing 4-substituted 1-H-Indole-3-glyoxyamides" the entire disclosure of which is incorporated herein by reference.

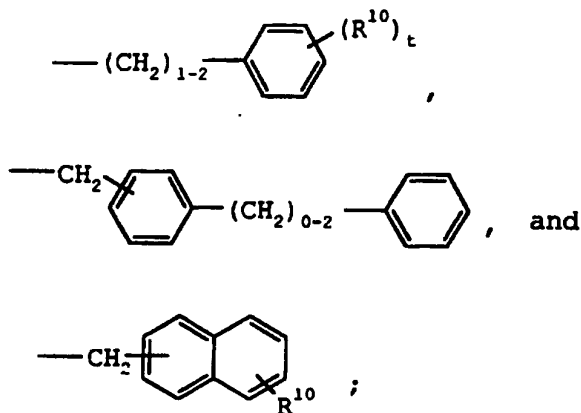
25 United States Patent Application Serial No. 09/105381 discloses the following process having steps (a) thru (i):
Preparing a compound of the formula (IZ) or a pharmaceutically acceptable salt or prodrug derivative
30 thereof

-30-



wherein:

- 5 R^1 is selected from the group consisting of -C₇-C₂₀ alkyl,



where

- 10 R^{10} is selected from the group consisting of halo, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, -S-(C₁-C₁₀ alkyl) and halo(C₁-C₁₀)alkyl, and t is an integer from 0 to 5 both inclusive;

- 15 R^2 is selected from the group consisting of hydrogen, halo, C₁-C₃ alkyl, C₃-C₄ cycloalkyl, C₃-C₄ cycloalkenyl, -O-(C₁-C₂ alkyl), -S-(C₁-C₂ alkyl), aryl, aryloxy and HET;

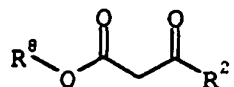
R^4 is selected from the group consisting of -CO₂H, -SO₃H and -P(O)(OH)₂ or salt and prodrug derivatives thereof; and

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R⁵, R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy, halo(C₂-C₆)alkyl, bromo, chloro, fluoro, iodo and aryl;

5 which process comprises the steps of:

a) halogenating a compound of formula X

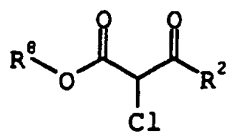


X

where R⁸ is (C₁-C₆)alkyl, aryl or HET;
with SO₂Cl₂ to form a compound of formula

10

IX

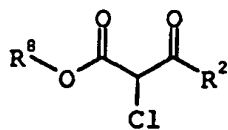


IX

;

b) hydrolyzing and decarboxylating a compound
of formula IX

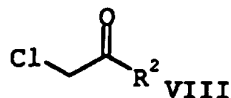
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IX

to form a compound of formula VIII

20

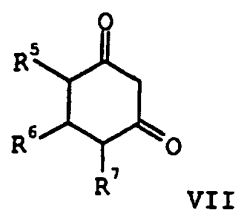


VIII

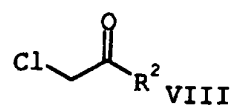
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c) alkylating a compound of formula VII

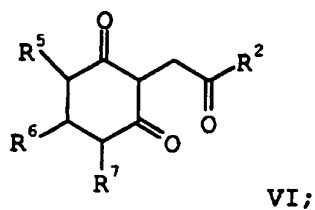


5 with a compound of formula VIII



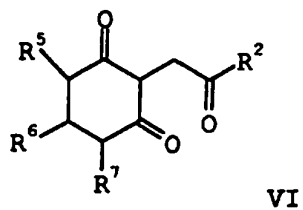
to form a compound of formula VI

10



d) aminating and dehydrating a compound of formula VI

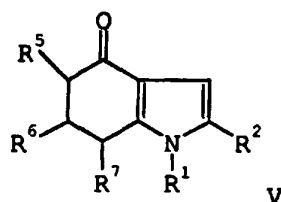
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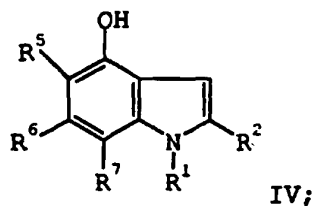
-33-

with an amine of the formula R^1NH_2 in the presence of a solvent that forms an azeotrope with water to form a compound of formula V;

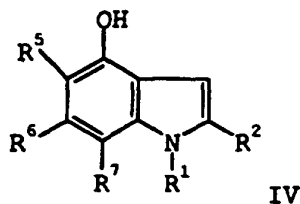
- 5 e) oxidizing a compound of formula V



- 10 by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IV



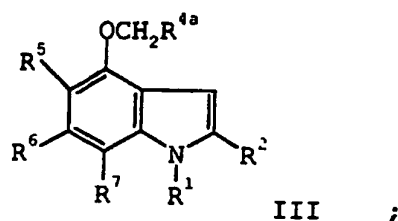
- 15 f) alkylating a compound of the formula IV



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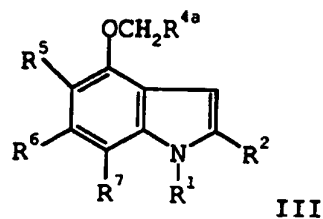
with an alkylating agent of the formula XCH_2R^{4a} where X is a leaving group and R^{4a} is $-CO_2R^{4b}$, $-SO_3R^{4b}$, $-P(O)(OR^{4b})_2$, or $-P(O)(OR^{4b})H$, where R^{4b} is an acid protecting group to form a compound of formula III

5



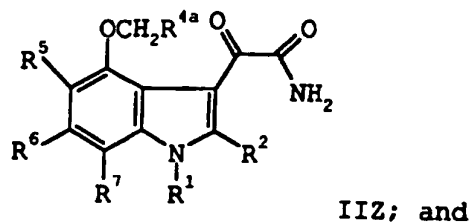
g) reacting a compound of formula III

10



with oxalyl chloride and ammonia to form a compound of formula IIZ

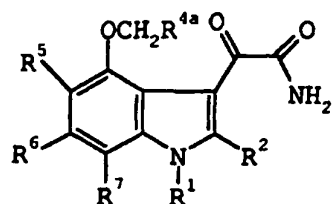
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h) optionally hydrolyzing a compound of formula IIZ

20

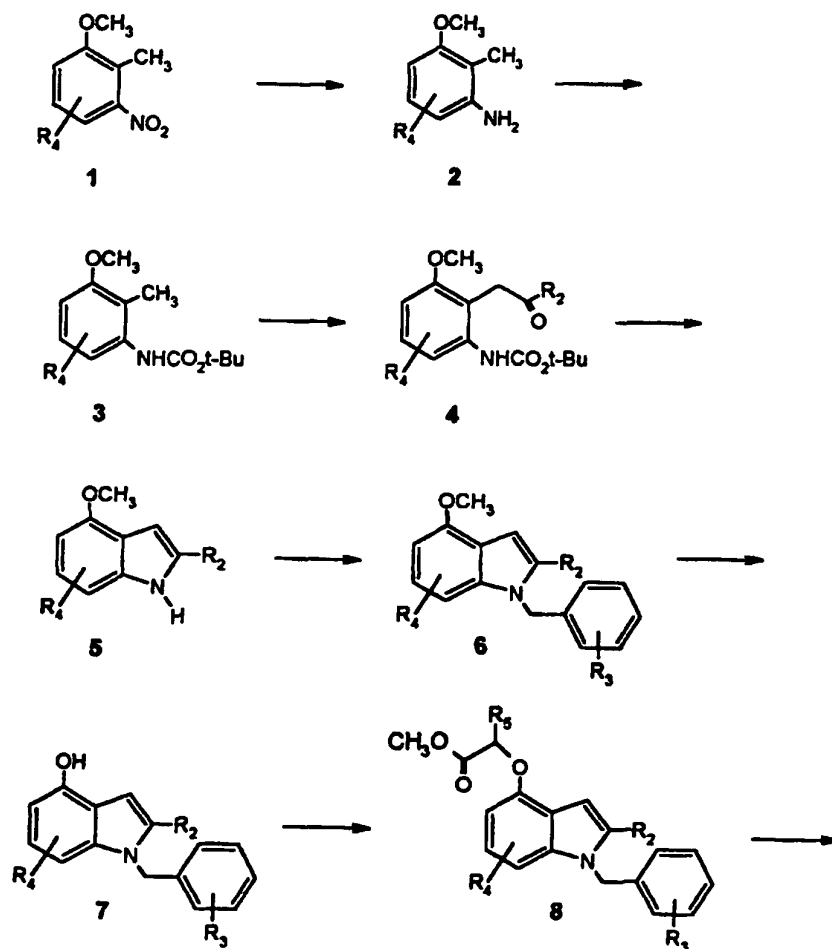
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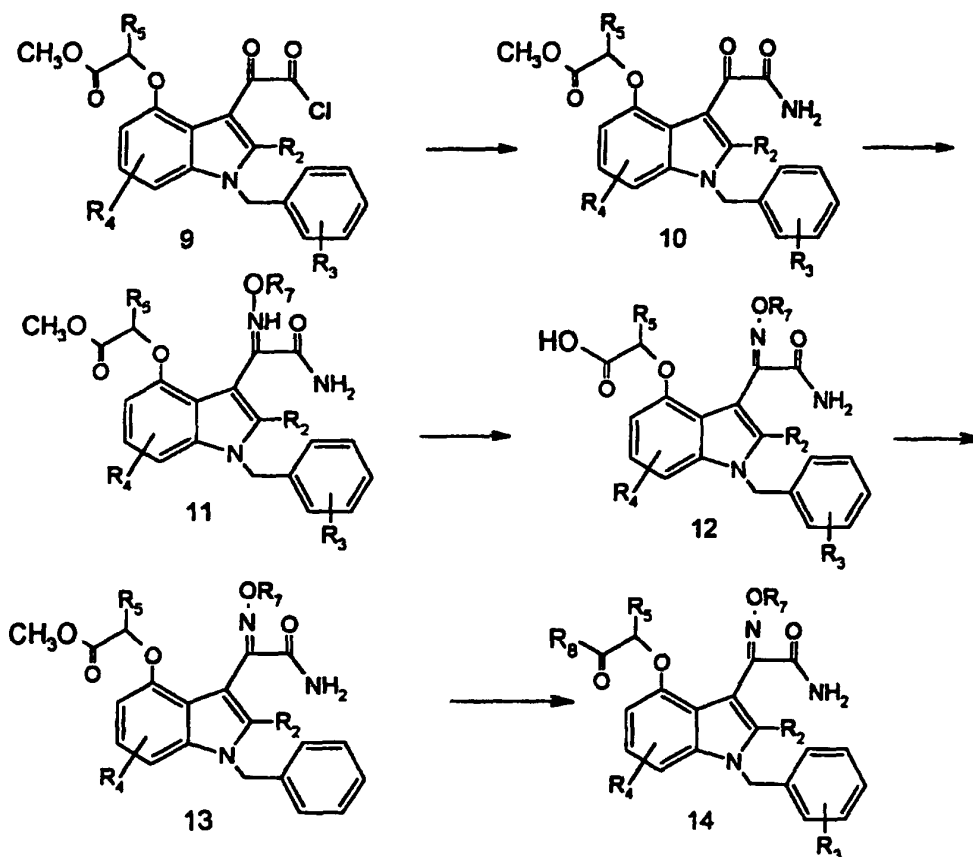
II Z

to form a compound of formula I.

- 5 Other synthesis procedures useful for the synthesis of the starting material are shown in the Scheme below:



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SYNTHESIS OF THE COMPOUNDS OF THE INVENTION:

- 5 The synthesis of indole oxime amides (compound of formula I, supra.) of this invention uses as starting material ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid (glyoxylamide), or a salt thereof (compound of formula
- 10 II, supra.). This starting material may be prepared by the reaction schemes or method of Example 1 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference). Similar methods are shown in European Patent Application No. 95302166.4,
- 15 Publication No. 0 675 110 (publ., 4 October 1995). Other

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conventional methods may also be used for preparing the starting material.

To obtain the 3-oxime amide-1H-indole compounds substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-metoxylaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline, 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative, 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-

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demethylated by stirring with boron tribromide in methylene chloride for approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated
5 herein by reference).

Compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is
10 incorporated herein by reference.

To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in the scheme *supra.*) is heated with hydroxylamine hydrochloride (when R₇ is H) in a THF/methanol mixture for 8 hours or until
15 the reaction was deemed complete. The reaction product was isolated by chromatography or other known laboratory procedure to afford a white solid in high yield. Substituted oximes such as when R₇ is methyl, ethyl, phenyl or other substituent can be prepared by reacting
20 the corresponding substituted hydroxylamine hydrochloride or free base with the glyoxylamide as described *supra.* The ester functionality at the 4 or 5 position on the indole nucleus can be: (1) converted to the acid by hydrolysis using lithium hydroxide or other known ester
25 hydrolysis methods or (2) to an amide functionality directly or via the acid functionality. The oxime thioamide analogs of the compounds of this invention can be made by substituting trimethylsilylthiocyanate for trimethylsilylisocyanate to produce the oxime thioamide
30 analog of compound 10, which can be hydrolyzed to the oxime thioamide-indole analog of compound 11. The oxime amides as well as the oxime thioamide compounds can also be isolated as the free acid or as its sodium salt.

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Methods of Using the Compounds of the Invention:

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA₂, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA₂ mediated release of fatty acids comprises contacting mammalian sPLA₂ with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, and related diseases which comprises administering to a mammal (including a human) a therapeutically effective dose of the indole compound of the invention (see, formulae I and II).

As previously noted the compounds of this invention are useful for inhibiting sPLA₂ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of sPLA₂ initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the

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formulation and not deleterious to the recipient thereof.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

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In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active ingredient. In tablets the Active ingredient is mixed

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with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingr dient	250
Starch, dried	200
Magnesium stearate	<u>10</u>

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Total 460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	<u>Quantity</u> <u>(mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

10 An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the
20 container.

Formulation 4

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Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

- 5 The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S.
- 10 sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are
- 15 compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

- 20 Capsules, each containing 80 mg of Active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

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The Active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

5

Formulation 6

Suppositories, each containing 225 mg of Active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

10

The Active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

15

Formulation 7

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

20

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a

25

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portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

- 5 An intravenous formulation may be prepared as follows:

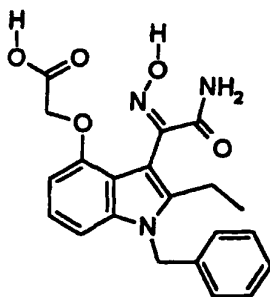
Active ingredient	100 mg
Isotonic saline	1,000 ml

- 10 The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

- 15 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

Example 1

2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid.

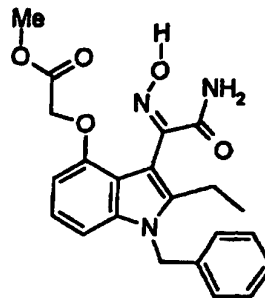


3A

20

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A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-

**2A**

yl]oxy]acetic acid methyl ester

A stirred mixture of 1 (600 mg, 1.52 mmol) and
 5 hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH₃OH (4 mL) was heated at 55 °C for 8 h. After concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH₂Cl₂) to give the title compound 2A (285 mg) as a white
 10 solid in 46% yield. IR (CHCl₃) 3510, 3415, 1757, 1667 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.84 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H),
 15 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (*M*⁺+1).

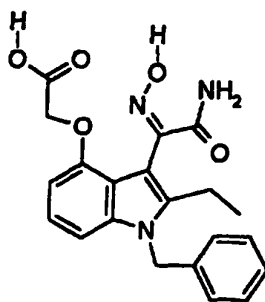
Elemental Analyses for C₂₂H₂₃N₃O₅·0.30(H₂O):

Calculated: C, 63.70; H, 5.73; N, 10.13;

Found: C, 63.68; H, 5.62; N, 10.20.

20 B. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

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Lithium hydroxide (4.17 N, 45.7 μ L, 0.191 mmol) and water (0.5 mL) were added to a stirred solution of **2A** (52.0 mg, 0.127 mmol) in THF (2 mL)/CH₃OH (2 mL). The mixture was stirred for 1.5 h to form a white suspension. THF (2 mL) was added to the suspension before it was treated with 5N HCl (50.8 μ L, 0.254 mmol) to form a clear solution. After organic solvents were evaporated, the wet solid residue was filtered, washed with water and dried to give the title compound **3A** (50.0 mg) as a white solid in 100% yield. IR (CHCl₃) 3475, 3425, 3366, 1703, 1634 cm⁻¹; ¹H-NMR (DMSO-d₆) δ 0.90-1.10 (m, 3H), 2.45-2.80 (m, 2H), 4.53 and 4.66 (both s, 2H), 5.39 (s, 2H), 6.30-6.50 (m, 1H), 6.84-7.00 (m, 4H), 7.10-7.55 (m, 5H), 11.32 and 11.38 (both s, 1H), 12.80 (br s, 1H); ESIMS *m/e* 396 (*M*⁺+1).

Elemental Analyses for C₂₁H₂₁N₃O₅·0.40(H₂O):

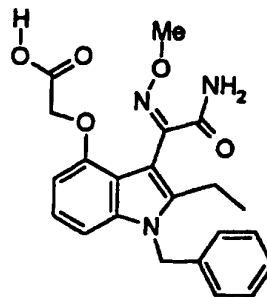
Calculated: C, 62.65; H, 5.46; N, 10.44;

Found: C, 62.73; H, 5.34; N, 10.35.

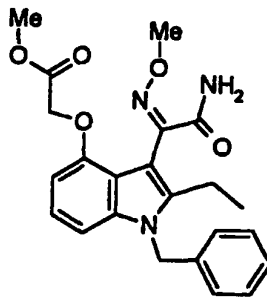
Example 2

2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

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**3B**

A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

**2B**

5

Following the experimental procedure as described in Example 1 Part A, 2B was synthesized from 1 and *O*-methylhydroxylamine hydrochloride as a white solid in 75% yield. IR (CHCl₃) 3476, 3344, 1756, 1678 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.18 (t, *J* = 7.5 Hz, 3H), 2.88 (q, *J* = 7.5 Hz, 2H), 3.83 (s, 3H), 3.99 (s, 3H), 4.71 (s, 2H), 5.31 (s, 2H), 5.60 (br s, 1H), 6.43 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.94-7.01 (m, 3H), 7.19-7.27 (m, 3H), 7.82 (br s, 1H); ESIMS *m/e* 424 (M⁺+1).

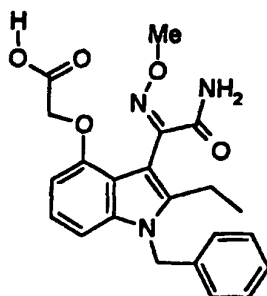
15 Elemental Analyses for C₂₃H₂₅N₃O₅:

Calculated: C, 65.24; H, 5.95; N, 9.92.

Found: C, 65.13; H, 5.72; N, 9.87.

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B. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid

**3B**

5 Following the experimental procedure as described in Example 1 Part B, **3B** was obtained as a white solid in 97% yield. IR (KBr) 3420, 3330, 3220, 1725, 1646 cm^{-1} ; $^1\text{H-NMR}$ (CDCl₃) δ 1.19 (t, $J = 7.5$ Hz, 3H), 2.86 (q, $J = 7.5$ Hz, 2H), 4.03 (s, 3H), 4.72 (s, 2H), 5.34 (s, 2H), 6.53 (d, $J = 7.9$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.99-7.05 (m, 3H), 7.23-7.32 (m, 3H), 7.53 (br s, 1H), 8.24 (br s, 1H); ESIMS m/e 410 ($\text{M}^+ + 1$).

Elemental Analyses for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5 \cdot 0.70(\text{H}_2\text{O})$:

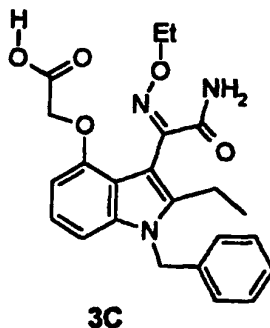
Calculated: C, 62.61; H, 5.83; N, 9.96;

15 Found: C, 62.64; H, 5.59; N, 9.86.

Example 3

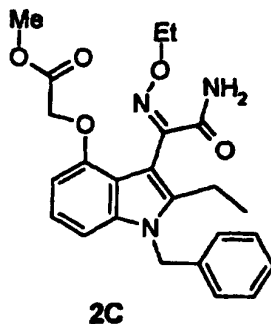
2-[[3-[[2-(Aminooxo)-1-(*N*-ethyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

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A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-ethyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

5



Following the experimental procedure as described in Example 1 Part A, 2C was synthesized from 1 and O-ethylhydroxylamine hydrochloride as a white solid in 66% yield. IR (CHCl₃) 3490, 3350, 1757, 1678 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.20 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 2.90 (q, J = 7.5 Hz, 2H), 3.84 (s, 3H), 4.27 (q, J = 7.0 Hz, 2H), 4.72 (s, 2H), 5.33 (s, 2H), 5.64 (br s, 1H), 6.45 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.96-7.02 (m, 3H), 7.20-7.30 (m, 3H), 7.82 (br s, 1H); ESIMS m/e 438 (M⁺+1).

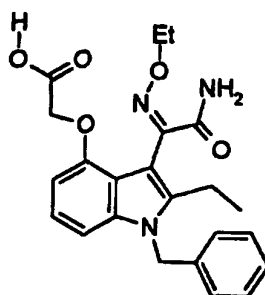
Elemental Analyses for C₂₄H₂₇N₃O₅:

Calculated: C, 65.89; H, 6.22; N, 9.60;

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Found: C, 66.06; H, 6.34; N, 9.59.

B. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-ethyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

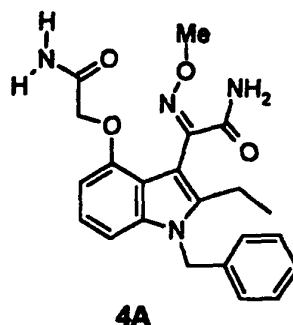
**3C**

Following the experimental procedure as described in Example 1 Part B, **3C** was obtained as a white solid in 95% yield. IR (CHCl₃) 3405, 3320, 3220, 1722, 1658 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.19 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 2.86 (q, *J* = 7.5 Hz, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.72 (s, 2H), 5.34 (s, 2H), 6.51 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.99-7.05 (m, 3H), 7.23-7.32 (m, 3H), 7.40 (br s, 1H), 8.14 (br s, 1H); ESIMS *m/e* 424 (M⁺+1).

Example 4

2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamide.

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Ammonia gas was bubbled through a stirred solution of **3B** (98.5 mg, 0.241 mmol) and benzotriazo-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (160 mg, 0.361 mmol) in DMF (2 mL) at ambient temperature under nitrogen. The mixture was stirred for 2 h with intermittent bubbling of ammonia gas. After concentration and subsequent chromatography on silica [gradient 0-10% CH₃OH in CH₂Cl₂/THF(1:1)], the title compound **4A** (80.2 mg) was obtained as a white solid in 81% yield. IR (KBr) 3441, 3427, 3275, 3212, 1633 cm⁻¹; ¹H-NMR (DMSO-d₆) δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.74 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 4.47 (s, 2H), 5.41 (s, 2H), 6.42-6.46 (m, 1H), 6.92-6.96 (m, 3H), 7.18-7.29 (m, 4H), 7.41 (s, 1H), 7.52 (s, 1H), 7.61 (s, 1H), 7.91 (s, 1H); ESIMS *m/e* 409 (M⁺+1).

Elemental Analyses for C₂₂H₂₄N₄O₄·0.40(CH₃OH):

Calculated: C, 63.87; H, 6.13; N, 13.30;

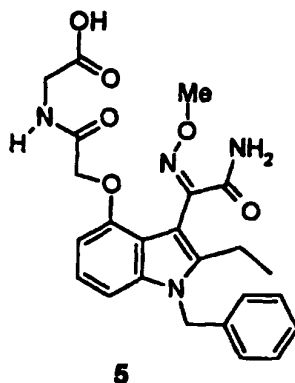
Found: C, 63.72; H, 6.03; N, 13.41.

20

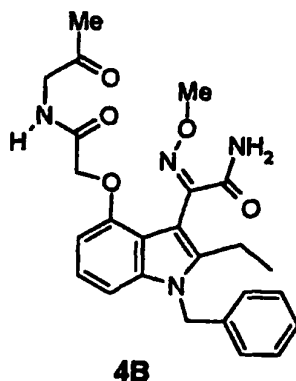
Example 5

2-[2-[[3-[[2-(Aminooxo)-1-(*N*-methoxyimino)ethyl]-2-thyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]acetic acid

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A. Preparation of 2-[2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetamido]acetic acid methyl ester



5

2,4,6-Collidine (0.0967 mL, 0.732 mmol) was added to a stirred solution of **3B** (100 mg, 0.244 mmol), glycine methyl ester hydrochloride (46.0 mg, 0.366 mmol) and benzotriazo-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (162 mg, 0.366 mmol) in DMF (2 mL) at ambient temperature under nitrogen. The mixture was stirred for 3 h. After concentration and subsequent chromatography on silica [gradient 0-50% THF/CH₂Cl₂ (1:1)], the title compound **4B** (118 mg) was obtained as a white solid in 100% yield. IR (CHCl₃) 3500, 3350, 3320, 1745, 1672 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.18 (t, *J* = 7.5 Hz,

-55-

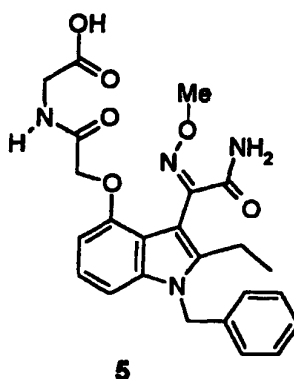
3H), 2.87 (q, $J = 7.5$ Hz, 2H), 3.73 (s, 3H), 4.04 (d, $J = 6.2$ Hz, 2H), 4.10 (s, 3H), 4.75 (s, 2H), 5.34 (s, 2H), 6.47 (d, $J = 7.9$ Hz, 1H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.96-7.04 (m, 3H), 7.22-7.32 (m, 4H), 7.34 (br s, 1H), 8.02 (br t, $J = 6.2$ Hz, 1H); ESIMS m/e 481 ($M^+ + 1$).

Elemental Analyses for $C_{25}H_{28}N_4O_6$:

Calculated: C, 62.49; H, 5.87; N, 11.66;

Found: C, 62.78; H, 5.55; N, 12.14.

- 10 B. Preparation of 2-[2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]acetic acid.



- Following the experimental procedure as described in
- 15 Example 1 Part B, 5 was obtained as a white solid in 97% yield. IR (KBr) 3415, 3400, 3000, 1767, 1665, 1633 cm^{-1} ; 1H -NMR (DMSO- d_6) δ 1.03 (t, $J = 7.4$ Hz, 3H), 2.74 (q, $J = 7.4$ Hz, 2H), 3.79 (s, 3H), 3.81 (d, $J = 6.2$ Hz, 2H), 4.58 (s, 2H), 5.41 (s, 2H), 6.49 (br t, $J = 4.2$ Hz, 1H), 6.92-6.97 (m, 4H), 7.18-7.28 (m, 3H), 7.59 (s, 1H), 7.85 (s, 1H), 8.52 (br t, $J = 6.2$ Hz, 1H), 12.60 (br s, 1H); ESIMS m/e 467 ($M^+ + 1$).

Elemental Analyses for $C_{24}H_{26}N_4O_6$:

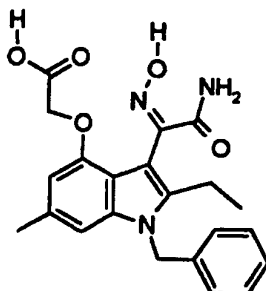
-56-

Calculated: C, 61.79; H, 5.62; N, 12.01;

Found: C, 61.91; H, 5.90; N, 11.94.

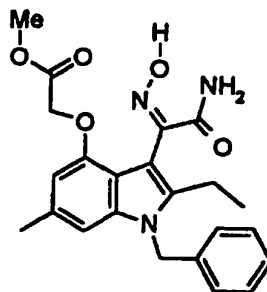
Example 6

- 5 2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid.



8A

- A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester.



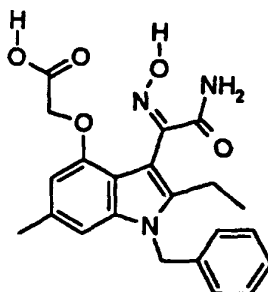
7A

- A stirred mixture of 6, 2-[[3-[[2-(Aminooxo)-1-(oxo)]ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester, (408.5 mg, 1.0 mmol), hydroxylamine hydrochloride (421 mg, 6.0 mmol) and anhydrous sodium acetate (492 mg, 6.0 mmol) in THF (3 mL)/CH₃OH (3 mL) was heated at reflux temperature for 5

-57-

- h. After concentration in vacuo at ambient temperature, the residue was dissolved in 10% THF/ethyl acetate, washed with H₂O, 1 N HCl, H₂O, saturated NaHCO₃ solution, H₂O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 100% EtOAc) to afford the title compound 7A (226 mg) as a white solid in 25% yield. IR (KBr, cm⁻¹) 3380, 3183, 1751, 1676, 1579 ; ¹H-NMR (CDCl₃)
- 5 δ 1.13 (t, *J* = 7.5 Hz, 3H), 2.34 (s, 3H), 2.79 (q, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 4.69 (s, 2H), 5.30 (s, 2H), 5.60 (br s, 1H), 6.22 (s, 1H), 6.30 (br s, 1H), 6.66 (s, 1H), 6.97 (d, *J* = 7.7 Hz, 2H), 7.21-7.29 (m, 4H); ESIMS *m/e* 424 (M⁺+1).
- 10
- 15 Elemental Analyses for C₂₃H₂₅N₃O₅:
- Calculated: C, 65.24; H, 5.95; N, 9.92;
- Found: C, 65.27; H, 5.95; N, 9.80.

- B. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.
- 20

**8A**

A mixture of 7A (85.0 mg, 0.2 mmol) and sodium hydroxide (1.0 N, 220 μ L, 0.22 mmol) in ethanol (5.0 mL) was

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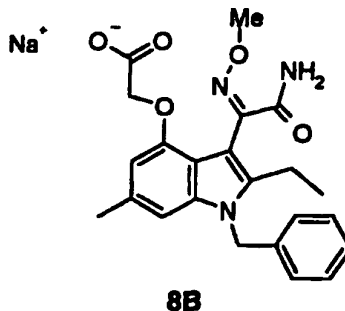
stirred for 1.5 h to form a colorless solution. The ethanol was removed in vacuo, the residue dissolved in water and ethyl acetate, and acidified to pH 2 with 1 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated to afford the title compound **8A** (44 mg) as a white solid in 54% yield. IR (KBr, cm^{-1}) 3488, 3372, 2520, 1690, 1610; $^1\text{H-NMR}$ (DMSO-d_6) δ 1.01 (t, J = 7.5 Hz, 3H), 2.27 (s, 3H), 2.67 (q, J = 7.5 Hz, 2H), 4.65 (s, 2H), 5.36 (s, 2H), 6.31 (s, 1H), 6.75 (s, 1H), 6.93 (d, J = 7.2 Hz, 2H), 7.17-7.28 (m, 3H), 7.52 (br s, 2H), 11.26 (s, 1H), 13.15 (br s, 1H); ESIMS m/e 410 ($\text{M}^+ + 1$).

Elemental Analyses for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5$:

Calculated: C, 64.54; H, 5.66; N, 10.26;
Found: C, 64.73; H, 5.34; N, 10.35.

Example 7

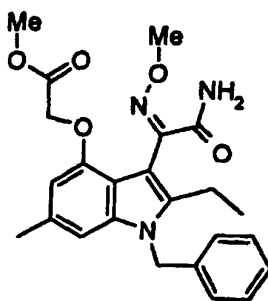
2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, sodium salt.



A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-methyloxyimino)ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-

-59-

1H-indol-4-yl]oxy]acetic acid methyl ester

**7B**

A stirred mixture of 6, 2-[[3-[[2-(Aminooxo)-1-(oxo)]ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, (408.5 mg, 1.0 mmol),
 5 O-methylhydroxylamine hydrochloride (501 mg, 6.0 mmol), and anhydrous sodium acetate (492 mg, 6.0 mmol) in THF (3 mL)/CH₃OH (3 mL) was heated at reflux temperature for 8 h. After concentration in vacuo at ambient temperature,
 10 the residue was dissolved in 10% THF/ethyl acetate, washed with H₂O, 1 N HCl, H₂O, saturated NaHCO₃ solution, H₂O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford the title compound 7B (435 mg) as a white solid in 99%
 15 yield. IR (KBr, cm⁻¹) 3378, 3178, 1756, 1678, 1577; ¹H-NMR (CDCl₃) δ 1.16 (t, *J* = 7.5 Hz, 3H), 2.33 (s, 3H), 2.84 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 3.99 (s, 3H), 4.69 (s, 2H), 5.28 (s, 2H), 5.58 (br s, 1H), 6.27 (s, 1H), 6.63 (s, 1H), 6.98 (d, *J* = 6.3 Hz, 2H), 7.19-7.27 (m, 3 H), 7.80 (br s, 1H); ESIMS *m/e* 438 (*M*⁺+1).

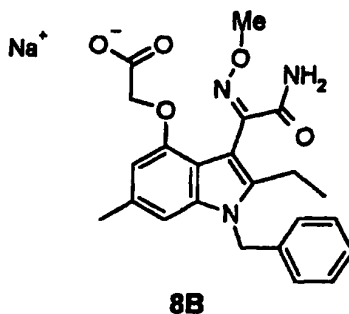
Elemental Analyses for C₂₄H₂₇N₃O₅:

Calculated: C, 65.89; H, 6.22; N, 9.60;

Found: C, 66.16; H, 6.27; N, 9.68.

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B. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-methoxyimino)]ethyl]-2-ethyl-6-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, sodium salt.



- 5 A suspension of **7B** (88.0 mg, 0.2 mmol) and sodium hydroxide (1.0 N, 220 μ L, 0.22 mmol) in ethanol (5.0 mL) was stirred for 0.5 h to form a hazy solution, and after 1.0 h a thick white precipitate had formed. After 3.0 h total stirring the resultant white precipitate was
- 10 collected by filtration, washed with small amounts of EtOH, diethyl ether, and hexanes, then dried in vacuo to afford the title compound **8B** (84mg) as a white solid in 94% yield. IR (KBr, cm^{-1}) 3353, 3230, 1667, 1604 ; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.03 (t, $J = 7.5$ Hz, 3H), 2.27 (s, 3H), 2.65 (q, $J = 7.5$ Hz, 2H), 3.75 (s, 3H), 4.05 (s, 2H), 5.33 (s, 2H), 6.26 (s, 1H), 6.66 (s, 1H), 6.92 (d, $J = 7.2$ Hz, 2H), 7.01 (br s, 1H), 7.19-7.27 (m, 3H), 10.11 (br s, 1H); ESIMS m/e 424 ($M^+ + 1$ carboxylic acid).

Elemental Analyses for $\text{C}_{23}\text{H}_{24}\text{N}_3 \text{NaO}_5$:

- 20 Calculated: C, 62.02; H, 5.43; N, 9.43;
Found: C, 64.57; H, 5.68; N, 9.85.

Assay

- The following chromogenic assay procedure was used
- 25 to identify and evaluate inhibitors of recombinant

-61-

human secreted phospholipase A₂. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A₂ on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

Reagents:

REACTION BUFFER -

CaCl₂·2H₂O (1.47 g/L)
KCl (7.455 g/L)
Bovine Serum Albumin (fatty acid free) (1 g/L)

(Sigma A-7030, product of Sigma Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)
pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

0.05 NaOAc.3H₂O, pH 4.5
0.2 NaCl
Adjust pH to 4.5 with acetic acid
DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

sn- racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-glycero-3-phosphorylcholine
TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

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TRITON X-100TM nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

- 5 The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100TM detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
- 10 2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
3. Add 50 nanograms of sPLA₂ (10 microliters) to appropriate wells;
4. Incubate plate at 40 °C for 30 minutes;
- 15 5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

All compounds were tested in triplicate.

- Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered
- 20 active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their
- 25 activity and, if sufficiently active, IC₅₀ values were determined. Typically, the IC₅₀ values (see, Table I, below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More
- 30 potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in
- 35 triplicate and result values were averaged for plotting and calculation of IC₅₀ values. IC₅₀ were determined

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by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

Results of Human Secreted Phospholipase A₂ Inhibition Tests

5

Table	
Compound of Example No.	Inhibition of human secreted PLA ₂ IC ₅₀ ± mean deviation (3-4 tests)
1	49nM

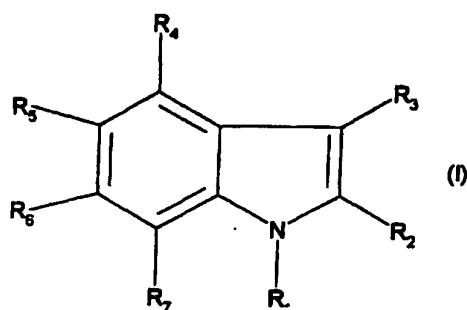
The compound of Example 1 is highly active in inhibiting sPLA₂.

10 While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

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WE CLAIM:

1. An indole compound represented by the formula
(I), or a pharmaceutically acceptable salt, solvate, or
5 prodrug derivative thereof;



wherein ;

- 10 R_1 is selected from groups (a), (b) and (c)
wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

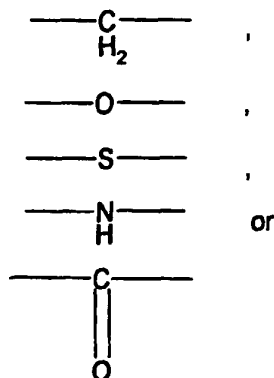
- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

- (c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and R_{11} is a group
20 selected from (a) or (b);

R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms;

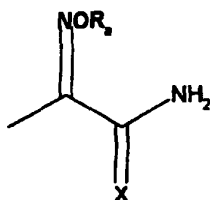
- R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected
25 from:

-65-



and Z is a oxime amide or oxime thioamide group represented by the formulae,

5



where X is oxygen or sulfur; and R_a is selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, C_1 to C_8 aralkyl and -CN.

- 10 R_4 and R_5 each independently selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$, where $-(L_a)-$, is a divalent acid linker having an acid linker length of 1 to 8; provided that at least one of R_4 and R_5 must be the group, -
- 15 $(L_a)-(acidic\ group)$;

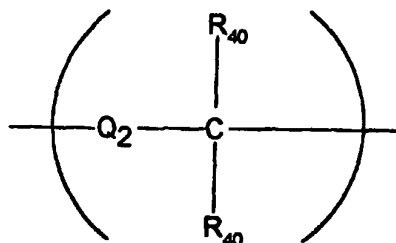
- R_6 and R_7 are each independently selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radical, and
- 20 heterocyclic radical substituted with non-interfering substituent(s).

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2. The compound of claim 1 wherein R_2 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3 \text{ alkyl})$, $-S-(C_1-C_3 \text{ alkyl})$, $-C_3-C_4$ cycloalkyl $-CF_3$, halo, $-NO_2$, $-CN$, or $-SO_3$.

5

3. The compound of Claim 1 wherein the acid linker group, $-(L_a)-$, for R_4 is selected from a group represented by the formula;



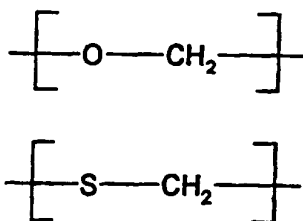
10

where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, $-C(O)-$, and $-S-$, and each R_{40} is independently selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, aralkyl, and halo.

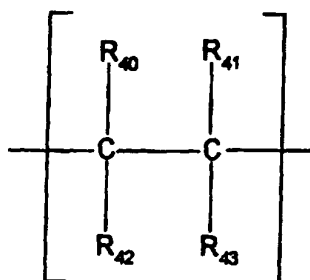
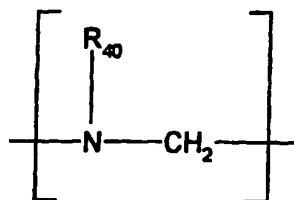
15

4. The compound of Claim 1 wherein the acid linker group, $-(L_a)-$, for R_4 is selected from $-(L_4)-$ is a divalent group selected from,

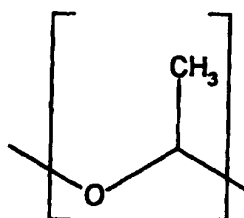
20



-67-



or

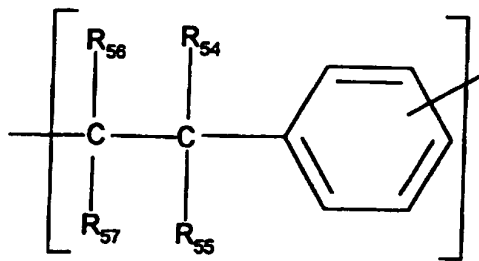
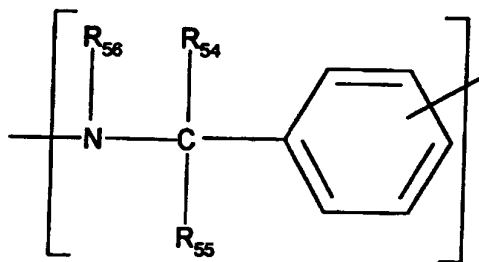
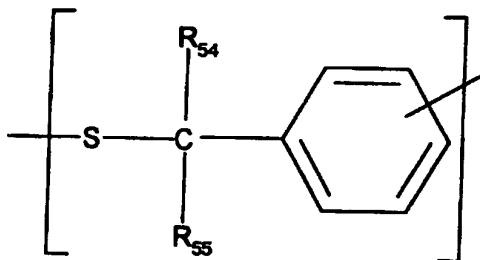
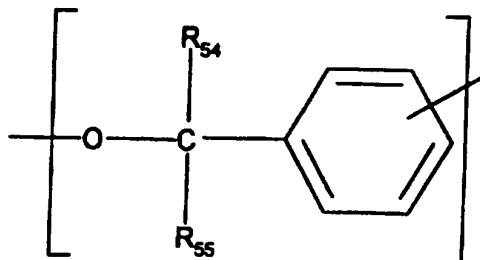


where R_{40} , R_{41} , R_{42} , and R_{43} are each independently
 5 selected from hydrogen, C_1 - C_8 alkyl.

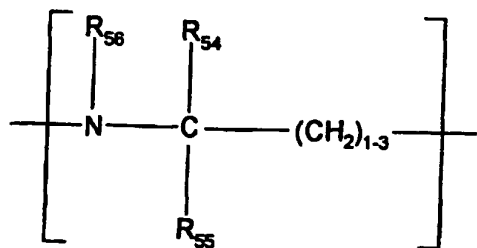
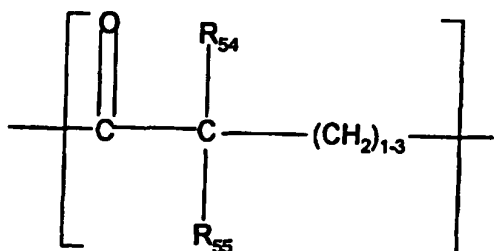
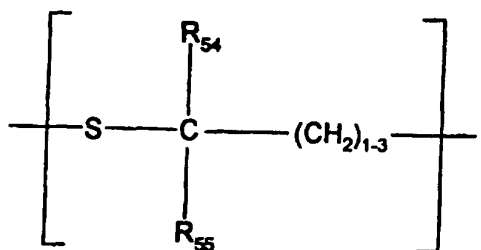
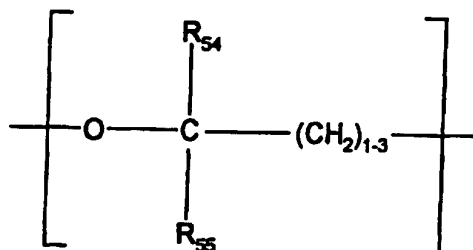
5. The compound of Claim 1 wherein the acid
 linker, $-(L_a)-$, for R_5 is selected from a group
 represented by the formulae consisting of;

10

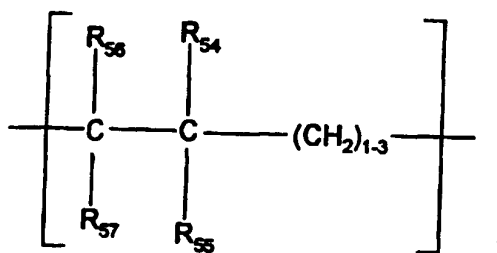
-68-



-69-



and



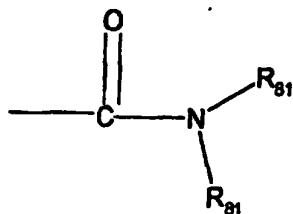
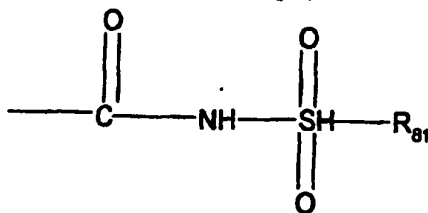
-70-

wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

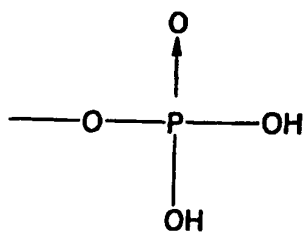
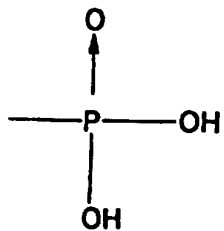
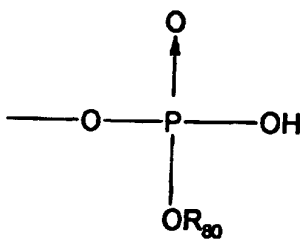
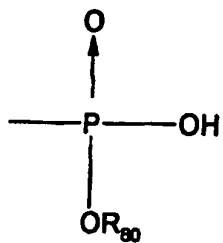
- 5 6. The compound of claim 1 wherein only one of R₄ and R₅ is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

-5-tetrazolyl,

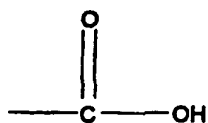
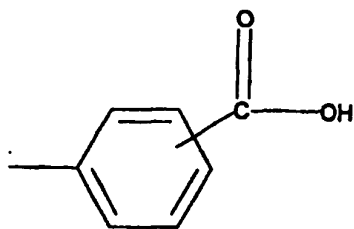
10

-SO₃H,

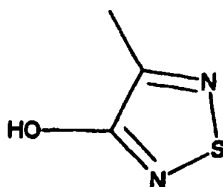
-71-



-72-



or

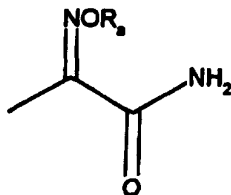


where R_{80} is a metal or C_1-C_8 alkyl and R_{81} is an organic substituent or $-CF_3$.

- 5 7. The compound of claim 6 wherein the (acidic group) is $-CO_2H$.

8. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;

10

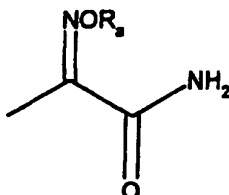


and the linking group $-(L_3)-$ is a bond; and R_a is hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

15

9. The compound of claim 1 wherein for R_3 , Z is the group r presented by the formula;

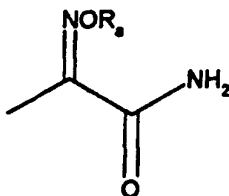
-73-



and the linking group $-(L_3)-$ is a bond; and R_a is hydrogen.

5

10. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



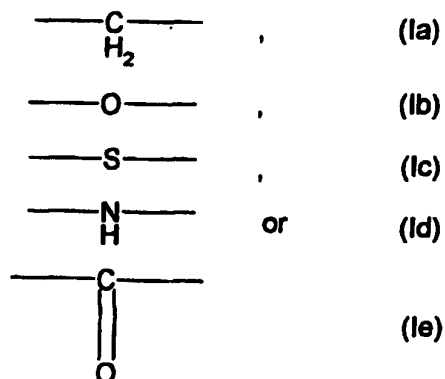
10 and the linking group $-(L_3)-$ is a bond; and R_a is selected from the group comprising methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, $-C(O)O(C_1-C_8 \text{ alkyl})$, $-(CH_2)_n-O-(C_1-C_8 \text{ alkyl})$, benzyloxy, phenoxy, phenylthio, $-(CONHSO_2R)$, -

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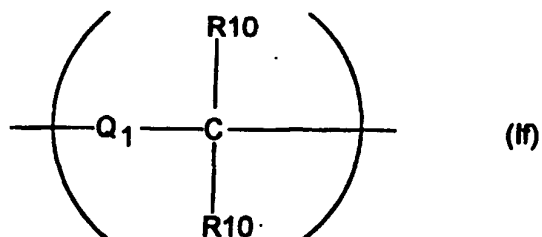
CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R_1 the divalent linking group $-(L_1)-$ is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):



15

or

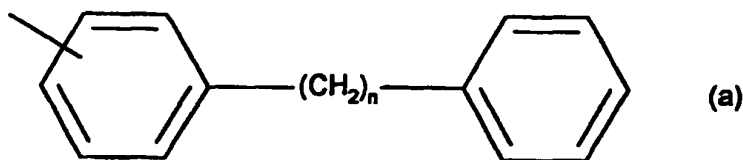


where Q_1 is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R_{10} is independently $-H$, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

-75-

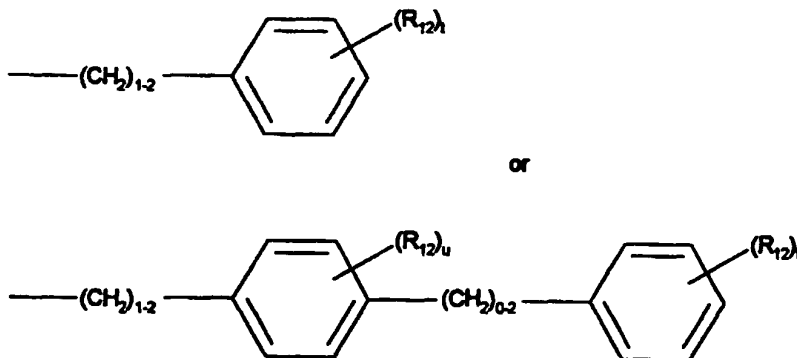
13. The compound of claim 1 wherein the linking group $-(L_1)-$ of R_1 is $-(CH_2)-$ or $-(CH_2-CH_2)-$.

14. The compound of claim 1 wherein for R_1 the group R_{11} is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by the formula (a):



where n is a number from 1 to 8.

15. The compound of Claim 12 wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the groups;



where R_{12} is a radical independently selected from halo, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, $-S-(C_1-C_{10}$ alkyl), and C_1 -

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C₁₀ haloalkyl, C₁-C₁₀ hydroxyalkyl and t is a number from 0 to 5 and u is a number from 0 to 4.

16. The compound of claim 1 wherein for R₁
- 5 the radical R₁₁ is a substituted or unsubstituted heterocyclic radical selected from pyrrolyl, pyrrolodiny, piperidiny, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl,
- 10 carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl,
- 15 benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinylmorpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
- 20 tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny, hexamethyleneiminium, heptamethyleneiminium, piperazinyl or quinoxalinyl.

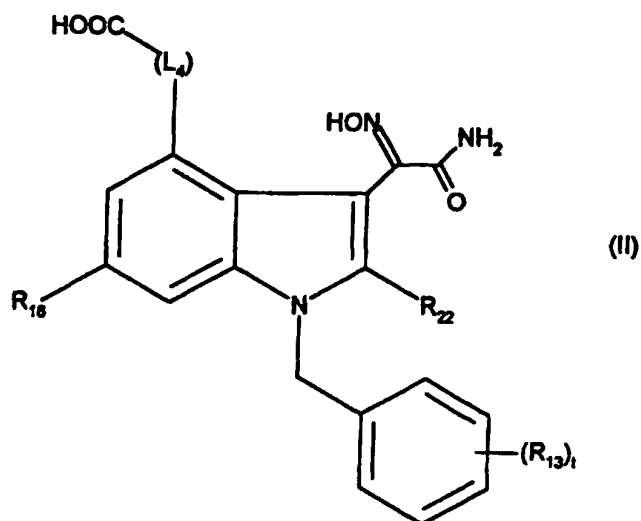
- 25 17. The compound of claim 1 in the form of a sodium salt.

18. The compound of claim 1 in the form of an ester prodrug.

30

19. An indole compound represented by the formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof;

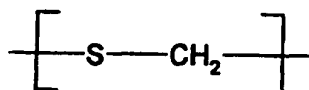
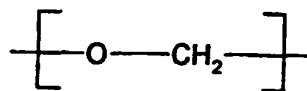
-77-



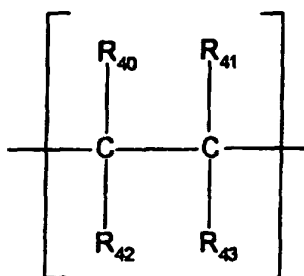
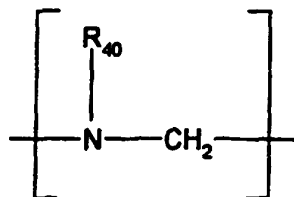
wherein ;

R₂₂ is selected from hydrogen, methyl, ethyl,
 5 propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or
 -O-CH₃;

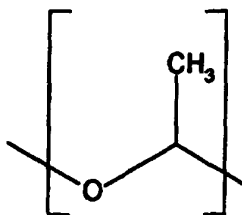
-(L₄)- is a divalent group selected from;



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or



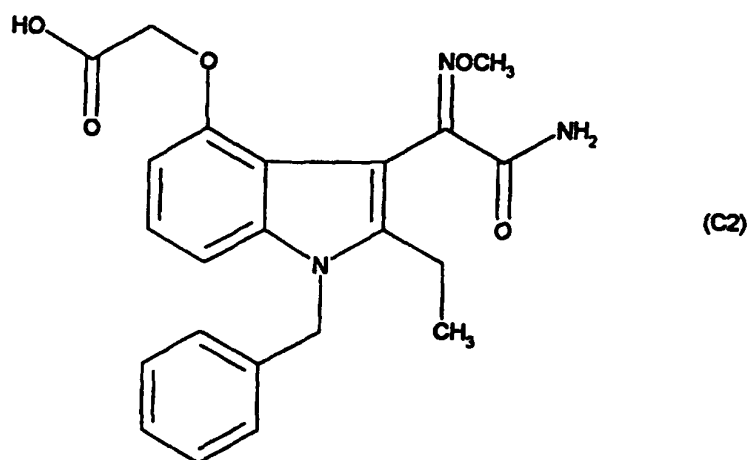
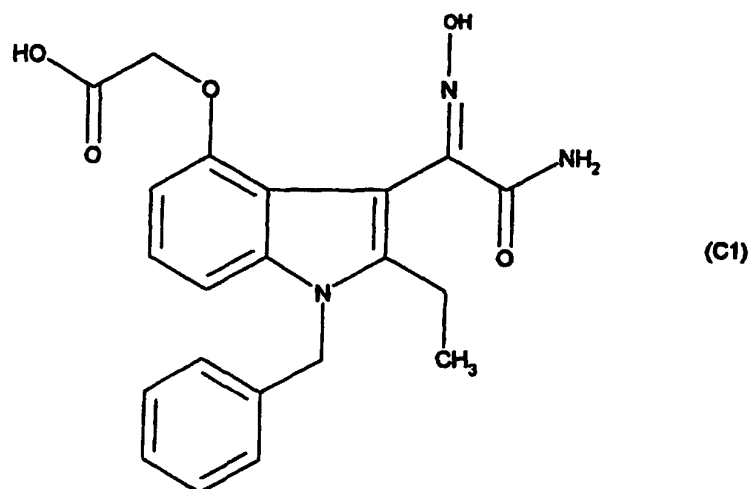
where R_{40} , R_{41} , R_{42} , and R_{43} are each independently
 5 selected from hydrogen or C₁-C₈ alkyl.

R_{16} is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈
 alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈
 hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈
 10 alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈, phenyl,
 halophenyl, hydroxyalkyl, and halo, and t is an integer
 from 0 to 5.

20. An indole compound represented by the formulae
 15 (C1), (C2) or (C3);

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5 or pharmaceutically acceptable salts or prodrugs thereof.

21. A pharmaceutical formulation comprising a
indole compound as claimed in claim 1 together with a
pharmaceutically acceptable carrier or diluent therefor.
10

22. A method of inhibiting sPLA₂ mediated release
of fatty acid which comprises contacting sPLA₂ with a

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therapeutically effective amount of indole compound as claimed in claim 1.

23. A method of treating a mammal, including a
5 human, to alleviate the pathological effects of
Inflammatory Diseases; wherein the method comprises
administration to said mammal of at least one indole
compound as claimed in Claim 1 in a pharmaceutically
effective amount.

10

24. A compound of claim 1 or a pharmaceutical
formulation containing an effective amount of the
compound of claim 1 in treatment of Inflammatory
Diseases.

15

25. A compound of claim 1 or a pharmaceutical
formulation containing an effective amount of the
compound of claim 1 for use as an inhibitor for
inhibiting sPLA₂ mediated release of fatty acid.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30405

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) C01B 21/16, C07D 209/14
US CL 423/407, 548/491

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. 423/407, 548/491

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,238,938 A (TONE et al.) 24 August 1993, col. 2, lines 10-20.	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents	* T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* E* earlier document published on or after the international filing date	* Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s), or which is cited to establish the publication date of another citation or other special reason (as specified)	* A* document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means	
* P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 MARCH 2000

Date of mailing of the international search report

04 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Authorized officer

DOMINIC KEATING

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30405

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1 ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2 ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3 ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

- 1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
- 3 ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos 1-25, in part

- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos :

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/30405

BOX II OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid

- Group I. The compounds of claim 1, formula (I) that contain hydrazine.
- Group II. The compounds of claim 1, formula (I) that contain morpholine, but not hydrazine
- Group III. The compounds of claim 1, formula (I) that contain pyrimidine, but not hydrazine or morpholine.
- Group IV. The compounds of claim 1, formula (I) that contain purine, but not hydrazine, morpholine or pyrimidine.
- Group V. The compounds of claim 1, formula (I) that contain quinoxaline, but not hydrazine, morpholine, pyrimidine or purine.
- Group VI. The compounds of claim 1, formula (I) that contain quinoline, but not hydrazine, morpholine, pyrimidine, purine or quinoxaline.
- Group VII. The compounds of claim 1, formula (I) that contain pyridine, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline or quinoline
- Group VIII. The compounds of claim 1, formula (I) that contain piperidine, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline or pyridine.
- Group IX. The compounds of claim 1, formula (I) that contain thiadiazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine or pyridine.
- Group X. The compounds of claim 1, formula (I) that contain thiazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine or thiadiazole
- Group XI. The compounds of claim 1, formula (I) that contain oxazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole or thiazole
- Group XII. The compounds of claim 1, formula (I) that contain triazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole or oxazole.
- Group XIII. The compounds of claim 1, formula (I) that contain phthalazine, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole or triazole.
- Group XIV. The compounds of claim 1, formula (I) that contain indazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole or phthalazine.
- Group XV. The compounds of claim 1, formula (I) that contain pyrazole or imidazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine or indazole.
- Group XVI. The compounds of claim 1, formula (I) that contain carbazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole or imidazole
- Group XVII. The compounds of claim 1, formula (I) that contain pyrrole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole or carbazole.
- Group XVIII. The compounds of claim 1, formula (I) that contain tetrazole, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole or pyrrole.
- Group XIX. The compounds of claim 1, formula (I) that contain pyrrolidine, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole or tetrazole.
- Group XX. The compounds of claim 1, formula (I) that contain azetidine, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole or pyrrolidine.
- Group XXI. The compounds of claim 1, formula (I) that contain thiophene, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole, pyrrolidine or azetidine.
- Group XXII. The compounds of claim 1, formula (I) that contain thioxane, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole, pyrrolidine, azetidine or thiophene.
- Group XXIII. The compounds of claim 1, formula (I) that contain dioxane, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole, pyrrolidine, azetidine, thiophene or thioxane.
- Group XXIV. The compounds of claim 1, formula (I) that contain furan, but not hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole, pyrrolidine, azetidine, thiophene, thioxane or dioxane.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/30405

Group XXV. The compounds of claim 1, formula (I) that do not contain hydrazine, morpholine, pyrimidine, purine, quinoxaline, quinoline, piperidine, pyridine, thiadiazole, thiazole, oxazole, triazole, phthalazine, indazole, pyrazole, imidazole, carbazole, pyrrole, tetrazole, pyrrolidine, azetidine, thiophene, thioxane, dioxane or furan.

Claims 1-25 will be examined commensurate in scope with the group elected.

The inventions listed as Groups I-XXV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the indole core is known in the art and therefore cannot be the special technical feature. The other substituents, such as the carbazole and pyrrole are structurally distinct.